(FILE 'HOME' ENTERED AT 13:33:32 ON 16 OCT 2000)

FILE 'MEDLINE, BIOSIS, CAPLUS, EMBASE, LIFESCI, SCISEARCH, TOXLINE, CABA, BIOTECHNO, CANCERLIT, ESBIOBASE' ENTERED AT 13:33:43 ON 16 OCT 2000

```
L1       4033 S IMPDH OR (INOSINE (W) MONOPHOSPHATE (W) DEHYDROGENASE?) OR (I
L2         24 S PYOGENES AND L1
L3         31 S L1 AND (STREPTOCOC? OR PYOGENES)
L4          7 DUP REM L3 (24 DUPLICATES REMOVED)
L5      66589 S (THREE (W) DIMENSIONAL (W) STRUCTUR?) OR (3D (W) STRUCTUR?) O
L6          0 S L1 AND L2 AND L5
L7      13789 S L5 AND ((CRYSTAL OR X-RAY OR (X(W)RAY)) (3W) STRUCTUR?)
L8         18 S L1 AND L3 AND ((CRYSTAL OR X-RAY OR (X(W)RAY)) (3W) STRUCTU
L9          3 DUP REM L8 (15 DUPLICATES REMOVED)
L10         0 S L4 AND L7
L11         3 S L4 AND ((CRYSTAL OR X-RAY OR (X(W)RAY)) (3W) STRUCTUR?)
L12         3 DUP REM L11 (0 DUPLICATES REMOVED)
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L4 ANSWER 1 OF 7 CAPLUS COPYRIGHT 2000 ACS

AN 1999:464100 CAPLUS

DN 131:83979

TI Method to identify specific inhibitors of ***inosine*** ***monophosphate*** ***dehydrogenase*** (***IMPDH***)

IN Collart, Frank R.; Huberman, Eliezer

PA The University of Chicago, USA

SO PCT Int. Appl., 34 pp.
CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9933996	A1	19990708	WO 1998-IB2109	19981223
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	AU 9915022	A1	19990719	AU 1999-15022	19981223
PRAI	US 1997-997758		19971224		
	WO 1998-IB2109		19981223		

AB This invention relates to methods to identify specific inhibitors of the purine nucleotide synthesis enzyme, ***IMPDH*** . ***IMPDH*** is an essential enzyme found in all free-living organisms from humans to bacteria and is an important therapeutic target. The invention allows the identification of specific inhibitors of any ***IMPDH*** enzyme which can be expressed in a functional form in a recombinant host cell. To illustrate the utility of the invention, the coding sequence of human and ***Streptococcus*** , ***pyogenes*** ***IMPDH*** were cloned into the pJF118EH expression vector. A variety of eukaryotic or prokaryotic host systems commonly used for the expression. . . prodn. Utilization of exogenous guanosine as a control component of the methods allows for the identification of inhibitors specific for ***IMPDH*** rather than other causes of decreased cell proliferation.

L4 ANSWER 2 OF 7 MEDLINE DUPLICATE 1

TI Characteristics and crystal structure of bacterial inosine-5'-monophosphate dehydrogenase.

AU Zhang R; Evans G; Rotella F J; Westbrook E M; Beno D; Huberman E; Joachimiak A; Collart F R

SO BIOCHEMISTRY, (1999 Apr 13) 38 (15) 4691-700.
Journal code: A0G. ISSN: 0006-2960.

AB ***IMP*** ***dehydrogenase*** (***IMPDH***) is an essential enzyme that catalyzes the first step unique to GTP synthesis. To provide a basis for the evaluation of ***IMPDH*** inhibitors as antimicrobial agents, we have expressed and characterized ***IMPDH*** from the pathogenic bacterium ***Streptococcus*** ***pyogenes*** . Our results show that the biochemical and kinetic characteristics of S. ***pyogenes*** ***IMPDH*** are similar to other bacterial ***IMPDH*** enzymes. However, the lack of sensitivity to mycophenolic acid and the Km for NAD (1180 microM) exemplify some of the differences between the bacterial and mammalian ***IMPDH*** enzymes, making it an attractive target for antimicrobial agents. To evaluate the basis for these differences, we determined the crystal. . . obtained with synchrotron radiation from the undulator beamline (19ID) of the Structural Biology Center at Argonne's Advanced Photon Source. S. ***pyogenes*** ***IMPDH*** is a tetramer with its four subunits related by a crystallographic 4-fold axis. The protein is composed of two domains:. . . flap as an essential catalytic element and indicate there are significant differences in the catalytic environment of bacterial and mammalian ***IMPDH*** enzymes. Comparison of the structure of bacterial ***IMPDH*** with the known partial structures from eukaryotic organisms will provide an explanation of their distinct properties and contribute to the design of specific bacterial ***IMPDH*** inhibitors

L4 ANSWER 3 OF 7 MEDLINE DUPLICATE 2

TI ***IMP*** ***dehydrogenase*** : mechanism of action and inhibition.

AU Hedstrom L

SO CURRENT MEDICINAL CHEMISTRY, (1999 Jul) 6 (7) 545-60. Ref: 89
Journal code: C02. ISSN: 0929-8673.

TI ***IMP*** ***dehydrogenase*** : mechanism of action and inhibition.

AB ***Inosine*** ***monophosphate*** ***dehydrogenase*** (***IMPDH***) catalyzes the conversion of IMP to XMP with the concomitant reduction of NAD to NADH. This reaction is the rate-limiting step in guanine nucleotide biosynthesis. ***IMPDH*** is a proven target for immunosuppressive, anticancer and antiviral chemotherapy, and may also be a target for antimicrobial agents. ***IMPDH*** is activated by monovalent cations, and one monovalent cation binding site appears to have been identified. The mechanism of ***IMPDH*** involves formation and hydrolysis of a covalent enzyme intermediate (E-XMP*) in a reaction reminiscent of glyceraldehyde-3-phosphate dehydrogenase. Substrates bind to ***IMPDH*** in a random order, hydride transfer is fast and NADH release precedes hydrolysis of E-XMP*. The hydrolysis of E-XMP* is. . .

L4 ANSWER 4 OF 7 MEDLINE DUPLICATE 3

TI Differential signatures of bacterial and mammalian ***IMP*** ***dehydrogenase*** enzymes.

AU Zhang R; Evans G; Rotella F; Westbrook E; Huberman E; Joachimiak A; Collart F R

SO CURRENT MEDICINAL CHEMISTRY, (1999 Jul) 6 (7) 537-43.
Journal code: C02. ISSN: 0929-8673.

TI Differential signatures of bacterial and mammalian ***IMP*** ***dehydrogenase*** enzymes.

AB ***IMP*** ***dehydrogenase*** (***IMPDH***) is an essential enzyme of de novo guanine nucleotide synthesis. ***IMPDH*** inhibitors have clinical utility as antiviral, anticancer or immunosuppressive agents. The essential nature of this enzyme suggests its therapeutic applications may be extended to the development of antimicrobial agents. Bacterial ***IMPDH*** enzymes show biochemical and kinetic characteristics that are different than the mammalian ***IMPDH*** enzymes, suggesting ***IMPDH*** may be an attractive target for the development of antimicrobial agents. We suggest that the biochemical and kinetic differences between. . . is a prerequisite for the rational identification of agents that specifically target the bacterial enzyme. We used sequence alignments of ***IMPDH*** proteins to identify sequence signatures associated with bacterial or eukaryotic ***IMPDH*** enzymes. These selections were further refined to discern those likely to have a role in catalysis using information derived from the bacterial and mammalian ***IMPDH*** crystal structures and site-specific mutagenesis. Candidate bacterial sequence signatures identified by this process include regions involved in subunit interactions, the. . . a secondary pattern of amino acid conservation associated with the major phylogenetic groups. Elucidation of the basis for this mammalian/bacterial ***IMPDH*** signature will provide insight into the catalytic mechanism of this enzyme and the foundation for the development of highly specific.

L4 ANSWER 5 OF 7 MEDLINE DUPLICATE 4
TI ***IMP*** ***dehydrogenase*** : structural aspects of inhibitor binding.
AU Goldstein B M; Colby T D
SO CURRENT MEDICINAL CHEMISTRY, (1999 Jul) 6 (7) 519-36. Ref: 118
Journal code: C02. ISSN: 0929-8673.
TI ***IMP*** ***dehydrogenase*** : structural aspects of inhibitor binding.
AB ***Inosine*** ***monophosphate*** ***dehydrogenase*** (***IMPDH*** , E.C. 1.1.1.205) is recognized as an important target for both antileukemic and immunosuppressive therapy. ***IMPDH*** catalyzes the NAD-dependent oxidation of inosine 5 monophosphate (IMP) to xanthosine 5 monophosphate. Several classes of ***IMPDH*** inhibitors are now in use or under development. These include agents that bind at either the substrate site (e.g. ribavirin. . . acid and thiazole-4-carboxamide adenine dinucleotide). All suffer from some degree of toxicity and/or susceptibility to metabolic inactivation. The finding that ***IMPDH*** exists as two isoforms, one of which (type II) is induced in tumor cells, has led to the search for potentially more effective isoform-specific agents. Recently, a number of crystal structures of ***IMPDH*** have become available. These include structures of the human type II, hamster, Tritrichomonas foetus, ***Streptococcus*** ***pyogenes*** and Borrelia burgdorferi enzymes. Each structure crystallizes as a tetramer of a/b barrels, with the active site located partly at. . .

L4 ANSWER 6 OF 7 MEDLINE DUPLICATE 5
TI Cloning, sequence analysis and expression of the group A ***streptococcal*** guaB gene encoding ***inosine*** ***monophosphate*** ***dehydrogenase*** .
AU Ashbaugh C D; Wessels M R
SO GENE, (1995 Nov 7) 165 (1) 57-60.
Journal code: FOP. ISSN: 0378-1119.
TI Cloning, sequence analysis and expression of the group A ***streptococcal*** guaB gene encoding ***inosine*** ***monophosphate*** ***dehydrogenase*** .
AB ***Inosine*** ***monophosphate*** ***dehydrogenase*** (***IMPDH***) is an essential enzyme in the biosynthesis of purines. We cloned a group A ***streptococcal*** (GAS) DNA fragment containing an open reading frame similar to other bacterial guaB genes encoding ***IMPDH*** . The GAS guaB consists of 1479 nucleotides encoding a protein of 493 amino acids. Expression of the GAS guaB in an Escherichia coli guaB mutant restored ***IMPDH*** activity, confirming the function of the gene product and demonstrating that the GAS enzyme is active in a heterologous bacterial. . .

L4 ANSWER 7 OF 7 CAPLUS COPYRIGHT 2000 ACS
TI A simple method for the rapid determination of the stereospecificity of NAD-dependent dehydrogenases applied to mammalian ***IMP*** ***dehydrogenase*** and bacterial NADH peroxidase
AU Cooney, David; Hamel, Ernest; Cohen, Marvin; Kang, Gil J.; Dalal, Maha; Marquez, Victor
SO Biochim. Biophys. Acta (1987), 916(1), 89-93
CODEN: BBACAQ; ISSN: 0006-3002
TI A simple method for the rapid determination of the stereospecificity of NAD-dependent dehydrogenases applied to mammalian ***IMP*** ***dehydrogenase*** and bacterial NADH peroxidase
AB The stereospecificity of ***IMP*** ***dehydrogenase*** (EC 1.1.1.205) from 2 different sources was detd. The enzyme prepns. were obtained from murine lymphoblasts and from Escherichia coli.. . . the enzyme from 2 very different species. In addn., the studies described here demonstrated that alc. dehydrogenase and NADH peroxidase (***Streptococcus*** faecalis), used as auxiliary enzymes, in combination with a microdistn. procedure, may rapidly det. the stereospecificity of any NAD-dependent dehydrogenase. . .

L9 ANSWER 1 OF 3 MEDLINE DUPLICATE 1
AN 1999218077 MEDLINE
DN 99218077
TI Characteristics and ***crystal*** ***structure*** of bacterial inosine-5'-monophosphate dehydrogenase.
AU Zhang R; Evans G; Rotella F J; Westbrook E M; Beno D; Huberman E; Joachimiak A; Collart F R
CS Center for Mechanistic Biology and Biotechnology, Argonne National Laboratory, 9700 South Cass Avenue, Argonne, Illinois 60439-4833, USA.. Fcollart@anl.gov
SO BIOCHEMISTRY, (1999 Apr 13) 38 (15) 4691-700.
Journal code: A0G. ISSN: 0006-2960.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
OS PDB-1ZFJ
EM 199907

L9 ANSWER 2 OF 3 MEDLINE DUPLICATE 2
AN 1999322381 MEDLINE
DN 99322381
TI Differential signatures of bacterial and mammalian ***IMP*** ***dehydrogenase*** enzymes.
AU Zhang R; Evans G; Rotella F; Westbrook E; Huberman E; Joachimiak A; Collart F R

CS Biosciences Division, Argonne National Laboratory.
SO CURRENT MEDICINAL CHEMISTRY, (1999 Jul) 6 (7) 537-43.
Journal code: C02. ISSN: 0929-8673.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199912
EW 19991203

L9 ANSWER 3 OF 3 MEDLINE DUPLICATE 3
AN 1999322380 MEDLINE
DN 99322380
TI ***IMP*** ***dehydrogenase*** : structural aspects of inhibitor binding.
AU Goldstein B M; Colby T D
CS Department of Biochemistry and Biophysics, University of Rochester Medical Center, Rochester, NY, 14642, USA.. barry_goldstein@urmc.rochester.edu
SO CURRENT MEDICINAL CHEMISTRY, (1999 Jul) 6 (7) 519-36. Ref: 118
Journal code: C02. ISSN: 0929-8673.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LA English
FS Priority Journals
EM 199912
EW 19991203

=> d l 14

L4 ANSWER 1 OF 7 CAPLUS COPYRIGHT 2000 ACS
AN 1999:464100 CAPLUS
DN 131:83979
TI Method to identify specific inhibitors of ***inosine*** ***monophosphate*** ***dehydrogenase*** (***IMPDH***)
IN Collart, Frank R.; Huberman, Eliezer
PA The University of Chicago, USA
SO PCT Int. Appl., 34 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9933996	A1	19990708	WO 1998-IB2109	19981223
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	AU 9915022	A1	19990719	AU 1999-15022	19981223
PRAI	US 1997-997758		19971224		
	WO 1998-IB2109		19981223		

RE.CNT 5
RE
(1) American Cyanamid Co; EP 0608722 A 1994
(2) Balzarini And De Clercq; BIOCHEMICAL JOURNAL 1992, V287, P785
(3) Carr; JOURNAL OF BIOLOGICAL CHEMISTRY 1993, V268(36), P27286 CAPLUS
(4) Pankiewicz; PHARMACOLOGY AND THERAPEUTICS 1997, V76(1-3), P89 CAPLUS
(5) Vertex Pharma; WO 9741211 A 1997

=> d kwic 1

L9 ANSWER 1 OF 3 MEDLINE DUPLICATE 1
TI Characteristics and ***crystal*** ***structure*** of bacterial inosine-5'-monophosphate dehydrogenase.
AB ***IMP*** ***dehydrogenase*** (***IMPDH***) is an essential enzyme that catalyzes the first step unique to GTP synthesis. To provide a basis for the evaluation of ***IMPDH*** inhibitors as antimicrobial agents, we have expressed and characterized ***IMPDH*** from the pathogenic bacterium ***Streptococcus*** ***pyogenes*** . Our results show that the biochemical and kinetic characteristics of S. ***pyogenes*** ***IMPDH*** are similar to other bacterial ***IMPDH*** enzymes. However, the lack of sensitivity to mycophenolic acid and the Km for NAD (1180 microM) exemplify some of the differences between the bacterial and mammalian ***IMPDH*** enzymes, making it an attractive target for antimicrobial agents. To evaluate the basis for these differences, we determined the ***crystal*** ***structure*** of the bacterial enzyme at 1.9 A with substrate bound in the catalytic site. The structure was determined using selenomethionine-substituted. . . obtained with synchrotron radiation from the undulator beamline (19ID) of the Structural Biology Center at Argonne's Advanced Photon Source. S. ***pyogenes*** ***IMPDH*** is a tetramer with its four subunits related by a crystallographic 4-fold axis. The protein is composed of two domains:. . . and a cystathione beta-synthase (CBS) dimer domain of so far unknown function. Using information provided by sequence alignments and the ***crystal*** ***structure*** , we prepared several site-specific mutants to examine the role of various active site regions in catalysis. These variants implicate the. . . flap as an essential catalytic element and indicate there are significant differences in the catalytic environment of bacterial and mammalian ***IMPDH*** enzymes. Comparison of the structure of bacterial ***IMPDH*** with the known partial structures from eukaryotic organisms will provide an explanation of their distinct properties and contribute to the design of specific bacterial ***IMPDH*** inhibitors.
CT Check Tags: Support, U.S. Gov't, Non-P.H.S.
Catalytic Domain
Crystallography, X-Ray
Dimerization
Enzyme Inhibitors: PD, pharmacology
****IMP Dehydrogenase: CH, chemistry***
*** IMP Dehydrogenase: GE, genetics***
*** IMP Dehydrogenase: ME, metabolism***
Models, Molecular
Mutagenesis, Site-Directed
Protein Conformation
Recombinant Proteins: CH, chemistry
Recombinant Proteins: GE, genetics
Recombinant Proteins: ME, metabolism
****Streptococcus pyogenes: EN, enzymology***

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CN   EC 1.1.1.205 (  ***IMP***      ***Dehydrogenase***  ); 0 (Enzyme
     Inhibitors); 0 (Recombinant Proteins)

=> d kwic 1 14

L4   ANSWER 1 OF 7  CAPLUS  COPYRIGHT 2000 ACS
TI   Method to identify specific inhibitors of   ***inosine***
       ***monophosphate***      ***dehydrogenase***   (  ***IMPDH***  )
AB   This invention relates to methods to identify specific inhibitors of the
     purine nucleotide synthesis enzyme,   ***IMPDH***  .    ***IMPDH***   is
     an essential enzyme found in all free-living organisms from humans to
     bacteria and is an important therapeutic target.  The invention allows the
     identification of specific inhibitors of any   ***IMPDH***   enzyme which
     can be expressed in a functional form in a recombinant host cell.  To
     illustrate the utility of the invention, the coding sequence of human and
       ***Streptococcus***  ,   ***pyogenes***      ***IMPDH***   were cloned into
     the pJF118EH expression vector.  A variety of eukaryotic or prokaryotic
     host systems commonly used for the expression.  .  . prodn.  Utilization
     of exogenous guanosine as a control component of the methods allows for
     the identification of inhibitors specific for   ***IMPDH***   rather than
     other causes of decreased cell proliferation.
ST   inhibitor   ***inosine***      ***monophosphate***      ***dehydrogenase***
     human
IT   Escherichia coli
        (H712, expression host; method to identify specific inhibitors of
        ***inosine***      ***monophosphate***      ***dehydrogenase***   (
        ***IMPDH***  ))
IT     ***Streptococcus***      ***pyogenes***
        (IMP-encoding gene from; method to identify specific inhibitors of
        ***inosine***      ***monophosphate***      ***dehydrogenase***   (
        ***IMPDH***  ))
IT   Bacillus subtilis
     Bacteria (Eubacteria)
     Eukaryote (Eukaryotae)
     Insect (Insecta)
     Neurospora
        (expression host; method to identify specific inhibitors of
        ***inosine***      ***monophosphate***      ***dehydrogenase***   (
        ***IMPDH***  ))
IT   Drug screening
     Molecular cloning
        (method to identify specific inhibitors of   ***inosine***
        ***monophosphate***      ***dehydrogenase***   (  ***IMPDH***  ))
IT   Drosophila
        (serani; method to identify specific inhibitors of   ***inosine***
        ***monophosphate***      ***dehydrogenase***   (  ***IMPDH***  ))
IT   118-00-3, Guanosine, biological studies
     RL: ANT (Analyte); BSU (Biological study, unclassified); ANST (Analytical
     study); BIOL (Biological study)
        (as a control component; method to identify specific inhibitors of
        ***inosine***      ***monophosphate***      ***dehydrogenase***   (
        ***IMPDH***  ))
IT   9028-93-7,   ***Inosine***      ***monophosphate***      ***dehydrogenase***
     RL: BSU (Biological study, unclassified); PRP (Properties); BIOL
     (Biological study)
        (method to identify specific inhibitors of   ***inosine***
        ***monophosphate***      ***dehydrogenase***   (  ***IMPDH***  ))
IT   367-93-1
     RL: BUU (Biological use, unclassified); BIOL (Biological study); USES
     (Uses)
        (method to identify specific inhibitors of   ***inosine***
        ***monophosphate***      ***dehydrogenase***   (  ***IMPDH***  ))

=> d hist

     (FILE 'HOME' ENTERED AT 13:33:32 ON 16 OCT 2000)

     FILE 'MEDLINE, BIOSIS, CAPLUS, EMBASE, LIFESCI, SCISEARCH, TOXLINE, CABA,
     BIOTECHNO, CANCERLIT, ESBIOBASE' ENTERED AT 13:33:43 ON 16 OCT 2000
L1         4033 S IMPDH OR (INOSINE (W) MONOPHOSPHATE (W) DEHYDROGENASE?) OR (I
L2           24 S PYOGENES AND L1
L3           31 S L1 AND (STREPTOCOC? OR PYOGENES)
L4            7 DUP REM L3 (24 DUPLICATES REMOVED)
L5        66589 S (THREE (W) DIMENSIONAL (W) STRUCTUR?) OR (3D (W) STRUCTUR?) O
L6            0 S L1 AND L2 AND L5
L7        13789 S L5 AND ((CRYSTAL OR X-RAY OR (X(W)RAY)) (3W) STRUCTUR?)
L8           18 S L1 AND L3 AND ((CRYSTAL OR X-RAY OR (X(W)RAY)) (3W) STRUCTU
L9            3 DUP REM L8 (15 DUPLICATES REMOVED)

=> s 14 and 117
<------User Break------>
u
SEARCH ENDED BY USER

=> s 14 and 17

L10           0 L4 AND L7

=> s 14 and ((crystal or x-ray or (x(w)ray)) (3w) structur?)

   3 FILES SEARCHED...
   9 FILES SEARCHED...
L11           3 L4 AND ((CRYSTAL OR X-RAY OR (X(W) RAY)) (3W) STRUCTUR?)

=> dup rem l11

PROCESSING COMPLETED FOR L11
L12           3 DUP REM L11 (0 DUPLICATES REMOVED)

=> d 1-3

L12  ANSWER 1 OF 3  MEDLINE
AN   1999218077     MEDLINE
DN   99218077
TI   Characteristics and   ***crystal***      ***structure***   of bacterial
     inosine-5'-monophosphate dehydrogenase.
AU   Zhang R; Evans G; Rotella F J; Westbrook E M; Beno D; Huberman E;
     Joachimiak A; Collart F R
CS   Center for Mechanistic Biology and Biotechnology, Argonne National
     Laboratory, 9700 South Cass Avenue, Argonne, Illinois 60439-4833, USA..
     Fcollart@anl.gov
SO   BIOCHEMISTRY, (1999 Apr 13) 38 (15) 4691-700.
     Journal code: A0G. ISSN: 0006-2960.
```

CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
OS PDB-1ZFJ
EM 199907

L12 ANSWER 2 OF 3 MEDLINE
AN 1999322381 MEDLINE
DN 99322381
TI Differential signatures of bacterial and mammalian ***IMP*** ***dehydrogenase*** enzymes.
AU Zhang R; Evans G; Rotella F; Westbrook E; Huberman E; Joachimiak A; Collart F R
CS Biosciences Division, Argonne National Laboratory.
SO CURRENT MEDICINAL CHEMISTRY, (1999 Jul) 6 (7) 537-43.
Journal code: C02. ISSN: 0929-8673.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199912
EW 19991203

L12 ANSWER 3 OF 3 MEDLINE
AN 1999322380 MEDLINE
DN 99322380
TI ***IMP*** ***dehydrogenase*** : structural aspects of inhibitor binding.
AU Goldstein B M; Colby T D
CS Department of Biochemistry and Biophysics, University of Rochester Medical Center, Rochester, NY, 14642, USA.. barry_goldstein@urmc.rochester.edu
SO CURRENT MEDICINAL CHEMISTRY, (1999 Jul) 6 (7) 519-36. Ref: 118
Journal code: C02. ISSN: 0929-8673.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LA English
FS Priority Journals
EM 199912
EW 19991203

=> d ti au so abs 2-3

L12 ANSWER 2 OF 3 MEDLINE
TI Differential signatures of bacterial and mammalian ***IMP*** ***dehydrogenase*** enzymes.
AU Zhang R; Evans G; Rotella F; Westbrook E; Huberman E; Joachimiak A; Collart F R
SO CURRENT MEDICINAL CHEMISTRY, (1999 Jul) 6 (7) 537-43.
Journal code: C02. ISSN: 0929-8673.
AB ***IMP*** ***dehydrogenase*** (***IMPDH***) is an essential enzyme of de novo guanine nucleotide synthesis. ***IMPDH*** inhibitors have clinical utility as antiviral, anticancer or immunosuppressive agents. The essential nature of this enzyme suggests its therapeutic applications may be extended to the development of antimicrobial agents. Bacterial ***IMPDH*** enzymes show biochemical and kinetic characteristics that are different than the mammalian ***IMPDH*** enzymes, suggesting ***IMPDH*** may be an attractive target for the development of antimicrobial agents. We suggest that the biochemical and kinetic differences between bacterial and mammalian enzymes are a consequence of the variance of specific, identifiable amino acid residues. Identification of these residues or combination of residues that impart this mammalian or bacterial enzyme signature is a prerequisite for the rational identification of agents that specifically target the bacterial enzyme. We used sequence alignments of ***IMPDH*** proteins to identify sequence signatures associated with bacterial or eukaryotic ***IMPDH*** enzymes. These selections were further refined to discern those likely to have a role in catalysis using information derived from the bacterial and mammalian ***IMPDH*** ***crystal*** ***structures*** and site-specific mutagenesis. Candidate bacterial sequence signatures identified by this process include regions involved in subunit interactions, the active site flap and the NAD binding region. Analysis of sequence alignments in these regions indicates a pattern of catalytic residues conserved in all enzymes and a secondary pattern of amino acid conservation associated with the major phylogenetic groups. Elucidation of the basis for this mammalian/bacterial ***IMPDH*** signature will provide insight into the catalytic mechanism of this enzyme and the foundation for the development of highly specific inhibitors.

L12 ANSWER 3 OF 3 MEDLINE
TI ***IMP*** ***dehydrogenase*** : structural aspects of inhibitor binding.
AU Goldstein B M; Colby T D
SO CURRENT MEDICINAL CHEMISTRY, (1999 Jul) 6 (7) 519-36. Ref: 118
Journal code: C02. ISSN: 0929-8673.
AB ***Inosine*** ***monophosphate*** ***dehydrogenase*** (***IMPDH*** , E.C. 1.1.1.205) is recognized as an important target for both antileukemic and immunosuppressive therapy. ***IMPDH*** catalyzes the NAD-dependent oxidation of inosine 5 monophosphate (IMP) to xanthosine 5 monophosphate. Several classes of ***IMPDH*** inhibitors are now in use or under development. These include agents that bind at either the substrate site (e.g. ribavirin and mizoribine) or at the NAD site (mycophenolic acid and thiazole-4-carboxamide adenine dinucleotide). All suffer from some degree of toxicity and/or susceptibility to metabolic inactivation. The finding that ***IMPDH*** exists as two isoforms, one of which (type II) is induced in tumor cells, has led to the search for potentially more effective isoform-specific agents. Recently, a number of ***crystal*** ***structures*** of ***IMPDH*** have become available. These include structures of the human type II, hamster, Tritrichomonas foetus, ***Streptococcus*** ***pyogenes*** and Borrelia burgdorferi enzymes. Each structure crystallizes as a tetramer of a/b barrels, with the active site located partly at the monomer-monomer interface. The substrate and cofactor bind in a continuous cleft on the C-terminal face of each barrel. The IMP base is well positioned to stack against the NAD nicotinamide ring to facilitate hydride transfer. The active site cleft is further bounded by a highly flexible flap and loop. These structures reveal enzyme-ligand interactions which suggest strategies for the design of improved inhibitors.